## REMARKS

Reconsideration is respectfully requested. Claims 42-52, 54-64, and 66 are pending. Claims 1-41 and 53 have been cancelled. Claim 65 has been withdrawn. Claims 42, 45, 49 and 65 have been amended. Support for the amended claims can be found for example on page 12 lines 26-32. New claim 66 has been added. Support for new claim 66 can be found for example on page 46 line 33 through page 47 line 10.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

### Election/Restriction

The Examiner has withdrawn claim 65 as directed to a constructively non-elected invention by original presentation. Applicant has amended claim 65 to include all limitations of the apparatus of currently amended claim 42. Upon allowance of claim 42, Applicant requests rejoinder of claim 65. MPEP § 806.05(i).

### Claim Rejections - 35 U.S.C. §102(e)

Claims 42-52, 54-64 and 66 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Blackburn et al., U.S. Patent No. 6,761,816 ("Blackburn I"). For an anticipation rejection under 35 U.S.C. §102 to be proper, a single reference must expressly or inherently disclose each and every element of a claim. In re Paulsen, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Blackburn I fails to disclose every limitation of the claimed invention.

Without acquiescing or admitting the Examiner's position, and solely to facilitate prosecution on the merits, Applicant has amended claim 42 to recite "wherein said inlet port and said outlet port are positioned to minimize the introduction or retention of air bubbles upon introduction of reagents" and claims 45 and 49 to recite "an inlet port positioned to minimize the introduction or retention of air bubbles upon the introduction of reagents." Claims 42, 45, and 49 recite a species of inlet and/or outlet port within the genus of ports. Blackburn I does not

disclose ports, as recited in the presently amended claims. As such, the present claims are not anticipated by Blackburn I. Applicant respectfully requests the withdrawal of this rejection.

Claims 42-47, 52, 54, 63 and 66 stand rejected under 35 U.S.C. §102(e) as anticipated by Wohlstader et al., U.S. Patent No. 6,207,369 ("Wohlstader"). For an anticipation rejection under 35 U.S.C. §102 to be proper, a single reference must expressly or inherently disclose each and every element of a claim. In re Paulsen, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Wohlstader fails to disclose every limitation of the claimed invention.

The Examiner asserts that

> Wohlstader et al teach the cartridge having inlet and outlet ports. Wohlstader further teach the cartridge is portable (Column 7, lines 46-54). Because the cartridge is portable the either port would be in the top or bottom at any given time based on the orientation of the cartridge at the time.
> [Page 4 of the Office Action]

In the section cited by the Examiner, Wohlstader discloses

> The means for sample delivery can be stationary or movable and can be any known in the art, including but not limited to one or more inlets, holes, pores, channels, pipes, microfluidic guides (e.g., capillaries), tubes, spigots, etc.
> [Col. 43 lines 51-55]

At most, the reference discloses a genus of inlets, holes, pores, channels, etc. As previously discussed, the disclosure of a genus does not inherently disclose all the species within that genus.

Without acquiescing or admitting the Examiner's position, and solely to facilitate prosecution on the merits, Applicant has amended claim 42 to recite "wherein said inlet port and said outlet port are positioned to minimize the introduction or retention of air bubbles upon introduction of reagents" and claims 45 and 49 to recite "an inlet port positioned to minimize the introduction or retention of air bubbles upon the introduction of reagents." Wohlstader does not disclose ports as recited in the presently amended claims. As such, the present claims are not anticipated by Wohlstader. Applicant respectfully requests the withdrawal of this rejection.

**Claim Rejections - 35 U.S.C. §103**

Claims 45-47, 55-57, 60-64 and 66 stand rejected 35 U.S.C. §102(e) as anticipated by Lennox et al., U.S. Patent No. 6,461,490 ("Lennox") as defined by Morris C. ed (Academy Press Dictionary of science and Technology, Academic Press, San Diego, 1992, page 1726) ("Morris") in view of Wohlstader. Applicant assumes the Examiner meant this rejection to be under 35 U.S.C. §103(a) as obvious, instead of under 35 U.S.C. §102(e) as anticipated. Therefore, Applicant has responded to the Examiner's rejection as though it was under 35 U.S.C. §103(a).

Claims 42-44, 46-52, 54-58, 60-64, and 66 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lennox as defined by Morris in view of Anderson et al., US Patent No. 6,326,211 ("Anderson") and Wohlstader. Claim 59 stands rejected over Lennox, as defined by Morris, in view of Anderson, and in further view of Hayes et al., U.S. Patent No. 6,334,980 ("Hayes").

35 U.S.C. § 103(a) requires that "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." To establish a *prima facie* case of obviousness, there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. The suggestion to make the claimed combination must be found in the prior art, and not based on applicants' disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

***1. Lennox modified in view of Wohlstader***

A. Modifying the reference would render it inoperable for its intended purpose.

The references provide no suggestion or motivation to modify their teachings to reach the present invention. M.P.E.P. §2145 III. provides that a "claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose." In addition, M.P.E.P §2143.01 V. provides that if a "proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)."

Claim 45 and those claims depending therefrom each require a "nucleic acid capture probe covalently attached to said electrode." The Examiner asserts

> It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to covalently attach the nucleic acid to the electrodes of Lennox. [Page 6 of the Office action]

However, the Examiner has not explained how such a modification would result in an operable invention. Specifically, the Examiner seems to ignore that fact that the nucleic acid of Lennox is already attached to the HSP2 protein component. Thus, the covalent attachment of the Lennox nucleic acid to the electrode in effect means that the HSP2 protein is attached to the electrode via the nucleic acid portion. As discussed further below, such a modification would render Lennox inoperable for its intended purpose.

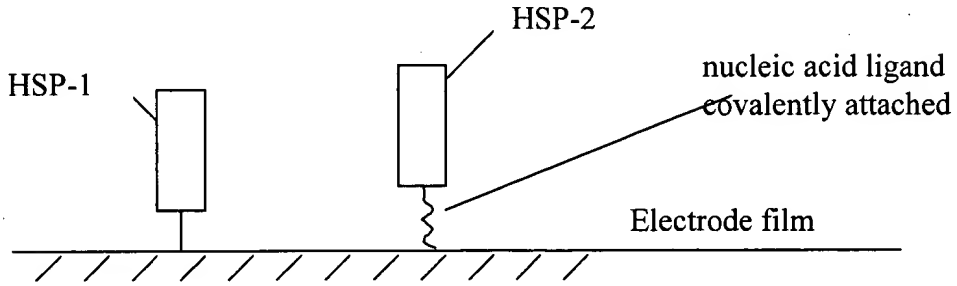
*1. Lennox requires the formation of the HSP1/HSP2 heterodimer*

Lennox discloses its intended purpose as "a biosensor apparatus for detecting a binding event between a ligand and a receptor." (Abstract). The reference discloses the HSP1 protein covalently attached to the electrode film. See Col. 8 lines 17-26. HSP2 is described as including an attached ligand which can be a nucleic acid. See Col. 8 lines 10-14 and lines 57-63. As disclosed and illustrated in Col. 10 lines 31-35 and Fig. 5A-B, the HSP2-containing ligand (59) is added to the covalently attached-HSP1 (58), resulting in binding of HSP1 and HSP2. This protein-protein interaction is dependent on a repeated heptad motif of conserved amino acid residues in each peptide's primary amino acid sequence. See Col. 6, lines 39-50.

*2. A modified Lennox would not form the HSP1/HSP2 heterodimer*

Lennox does not disclose the attachment of a nucleic acid to an electrode film. Rather, the reference is limited to describing a nucleic acid attached to HSP-2. If, as the Examiner asserts, a person of ordinary skill in the art were to covalently attach a nucleic acid to the electrode of Lennox, heterodimer formation would be prevented. The reference discloses that HSP2-containing ligand (e.g. a nucleic acid) is added to the electrode-anchored HSP1 and heterodimer formation occurs. In other words, free HSP2 is added to electrode-bound HSP1 to form a heterodimer. If, as the Examiner asserts and as illustrated below, the nucleic acid portion

of HSP2 is covalent attached to the electrode film, heterodimer formation would not occur because both HSP1 and HSP2 are electrode-bound.




*3. Preventing HSP1/HSP2 heterodimer formation renders Lennox inoperable*

Lennox states that heterodimer formation enhances the close packed structure of the monolayer as shown by the drop in conductance in Fig. 7. See Col. 12 lines 13-19. Lennox discloses the importance of the role of the close packed monolayer in the operation of the biosensor:

> The triggering event in the biosensor is the binding of a ligand-binding agent to the surface-bound ligand. This binding perturbs the ordered structure of the monolayer sufficiently to allow the movement of redox species through the monolayer, producing current through the electrode. Measurements performed in support of the invention indicate that one triggering event leads to $10^2$ to $10^6$ ionic and electron transfer events per second, and thus is highly multiplicative. The biosensor records this binding event as an increase in current across the electrode, i.e., between the working and counter electrodes. [See Col. 12 lines 51-61]

If no HSP1/HSP2 heterodimers are present, then the low conductance monolayer required by Lennox will not be formed. Under such conditions, the binding of a ligand-binding agent to the HSP2 nucleic acid portion would be undetectable and binding events would not be recorded by the biosensor. Therefore, a modified Lennox in view of Wohlstader would render Lennox inoperable for its intended purpose and therefore is not sufficient to render the claims prima facie obvious.

B. Modifying the invention would change Lennox's principle of operation

MPEP §2143.01 VI provides that if "the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then

the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)." As previously discussed, the Examiner argues that it would have been obvious to modify Lennox view of Wohlstader to reach a "capture probe nucleic acid covalently attached to said electrode" as recited in claim 45 and those claims depending therefrom. However, the Examiner has not explained how such a modification would avoid fundamentally changing Lennox's principle of operation.

As discussed above, Lennox's HSP2-containing ligand (which may be a nucleic acid) is added to the covalently attached-HSP1, resulting in binding of HSP1 and HSP2 through the repeated heptad motif of conserved amino acid residues common to each peptide's amino acid sequence. If a person of ordinary skill in the art were to modify the HSP2 nucleic acid component so as to covalently attach it to the electrode film, the HSP components would be unable to interact. Lennox illustrates its principle of operation as a biosensor in Fig. 1A and 1B. Specifically, the reference discloses

> The apparatus includes a reaction chamber 22 defined in part by a substrate 24 which has a biosensor surface 26 within the chamber. The biosensor surface has attached thereto, two-subunit heterodimer complexes, such as complexes 28, each complex carrying a ligand, such as ligands 30, which forms one of the two binding pairs of a ligand/anti-ligand agent whose binding serves as the "trigger" of a measurable biosensor event, as will be described below. FIG. 1B shows the condition of the biosensor surface after binding of ligand-binding agent, such as indicated at 34, to a portion of the ligands on the biosensor surface. The two peptides are constructed, as will be detailed below; for self-assembly into stable, two-subunit alpha-helix coiled-coil heterodimer complexes, and when so assembled, serve to anchor the ligand on the biosensor surface as shown.
> [Col. 5 lines 15-36]

According to Lennox, heterodimer formation is required to present the ligand (30) on the biosensor surface (26). If Lennox is modified to reach "nucleic acid capture probe covalently attached to said electrode" as required by the present invention, heterodimer formation would be prevented. As discussed previously, heterodimer formation is critical for Lennox's system of detection. Therefore, preventing heterodimer formation would impermissibly alter Lennox's principle of operation. Thus, modifying Lennox in view of Wohlstader to reach the claimed invention fundamentally changes the principle of operation of the cited reference. Because "the proposed modification cannot change the principle of operation of a reference" under M.P.E.P

§2143.01 VI, Lennox modified in view of Wohlstader is not sufficient to render the claims prima facie obvious.

*2. Lennox modified in view of Anderson and Wohlstader.*

Claims 42, 45, 49, and those claims depending therefrom each require a "nucleic acid capture probe covalently attached to said electrode." As previously discussed, the modification of Lennox in view of Wohlstader would result in the prevention of heterodimer formation. This modification would both (i) render Lennox inoperable for its intended purpose and (ii) change its principle of operation and therefore the same arguments apply to this rejection.

For all the reasons cited above, the cited references in combination fail to render the claims obvious. Applicant respectfully request that this ground for rejection be withdrawn.

*3. Lennox modified in view of Anderson and Wohlstader, and in further view of Hayes.*

Claim 59 has been rejected as obvious over these references. Claim 59 depends from claim 58, which depends from claim 42, 45, or 49. As such, claim 59 also requires a "nucleic acid capture probe covalently attached to said electrode." As previously discussed, the modification of Lennox in view of Wohlstader would result in the prevention of heterodimer formation. This modification would both (i) render Lennox inoperable for its intended purpose and (ii) change its principle of operation and therefore the same arguments apply to this rejection.

For all the reasons cited above, The cited references in combination fail to render the claims obvious. Applicant respectfully request that this ground for rejection be withdrawn.

**Claim Rejections – Double Patenting**

Claims 42-52, 54-64 and 66 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of Blackburn I in view of Lennox.

Claims 42-52, 54-64, and 66 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10-12, 14-16, and 32-34 of Blackburn et al., allowed U.S. Application No. 09/712,792 ("Blackburn II").

Claims 42-52, 54-64, and 66 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 15-24 of copending U.S. Application No. 10/412,660 ("Terbrueggen").

***1. Blackburn I in view of Lennox.***

A. The Legal Standard for Obviousness-Type Double Patenting

In an obviousness-type double patenting rejection, the Examiner must show that the rejected claims are an obvious variant of the claims of the cited patent. Double patenting requires a comparison of the claims at issue with the claims of the issued patent. M.P.E.P. § 804 III provides:

> [a] double patenting rejection must rely on a comparison with the claims in an issued or to be issued patent, whereas an obviousness rejection based on the same patent under 35 U.S.C. § 102(e)/103(a) relies on a comparison with what is disclosed (whether or not claimed).

An obviousness type double patenting rejection is "'analogous to a failure to meet the non-obviousness requirement of 35 U.S.C. 103 except that the patent principally underlying the double patenting rejection is not considered prior art." M.P.E.P. § 804 I.

B. The Legal Standard Applied to the Present Rejection

As currently amended, claims 42, 45, 49, and those claims depending therefrom require a port "positioned to minimize the introduction or retention of air bubbles upon introduction of reagents." The Examiner has cited claims 1-16 from Blackburn I and Lennox to make this rejection. However, she acknowledges that the "claim sets . . . differ in that the instant claims define the cartridge . . . [as] having inlet and/or outlet ports." In an attempt to cure the defects of Blackburn I the Examiner asserts

> However, cartridges having ports were well known and routinely practiced in the art at the time the claimed invention was made as taught by Lennox et al who teach that ports permit introduction of sample into the closed chamber (Column 5, lines 37-41). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the patent cartridge with the ports of Lennox et al to arrive . . . [at the] instantly claimed invention.
> [Page 14-15 of the Office Action]

The Applicant respectfully disagrees and submits that the Examiner has not established a *prima facie* case for obviousness-type double patenting. The Examiner improperly relies on

Lennox's disclosure rather its claims. A double patenting rejection must be based on a comparison of the claims in the issued patent. The Examiner cites the specification of Lennox, i.e. Column 5, lines 37-41, rather than its claims. Blackburn I's claims are properly cited by the Examiner but lack the port requirement of the present invention.

In sum, the cartridges of claims 42, 45, 49, and those claims depending therefrom are not obvious variants of the devices of claims 1-16 of Blackburn I. The Examiner impermissibly relies on the Lennox disclosure rather than its claims. Applicants respectfully request that this rejection be withdrawn.

***2. Blackburn II.***

As currently amended, claims 42, 45, 49, and those claims depending therefrom include the requirement of a port "positioned to minimize the introduction or retention of air bubbles upon introduction of reagents." The present claims are not obvious variants of the claims of Blackburn II. The Examiner asserts that

> The claims sets merely differ in the arrangement of limitations within the claim sets and terminology used to describe elements of the cartridge. For example, . . . [the] instant claims define the chamber as having a port while the '792 claim sets define a channel, both the channel and port are defined by a filter membrane. Therefore, the claims sets are drawn to cartridges that are not patentably distinct. [Page 15 of the Office Action]

However, Blackburn II's allowed claims do not include the port "positioned to minimize the introduction or retention of air bubbles upon introduction of reagents" requirement. As such, the present claims are non-obvious variants of Blackburn's claims. Applicants respectfully request that this rejection be withdrawn.

**3. Terbrueggen.**

Under M.P.E.P. § 804 I. B. 1. Nonstatutory Double Patenting Rejections, if a

> "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue without a terminal disclaimer.

The present application was filed before Terbrueggen. At present, the claims of Terbrueggen do not include a provisional nonstatutory obviousness-type double patenting rejection. Based on the Applicant's previous arguments, the Terbrueggen rejection is the only one remaining in the present application. As such, the Applicant requests the withdrawal of this rejection under § 804 I. B. 1. without a terminal disclaimer.

## Conclusion

Applicants submit the claims are in condition for allowance, and notification of such is respectfully requested. If after review, the Examiner feels there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

Respectfully submitted,

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